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DIELS-ALDER REACTIONS IN ETHYLAMMONIUM NITRATE, A LOW-MELTING FUSED SALT

David A. Jaeger* and Charles E. Tucker

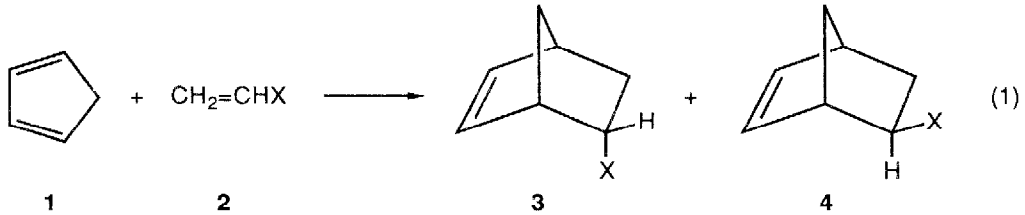
Department of Chemistry, University of Wyoming, Laramie, WY 82071

Summary: Relative to nonpolar organic solvents, ethylammonium nitrate gave endo stereoselectivity enhancements for the Diels-Alder reactions of cyclopentadiene with methyl acrylate and methyl vinyl ketone.

Ethylammonium nitrate (EAN) is a low-melting (mp *ca.* 12 °C) fused salt that shares some, but not all of the characteristic features of water.[1,2] As a result, the enzyme alkaline phosphatase is active in EAN-water mixtures.[3] Also, in EAN single-chain surfactants form micelles with critical micelle concentrations (cmc's) only five to ten times greater than those in water,[4] and phospholipids form bilayer structures.[5] Indeed, EAN resembles water in those properties associated with the hydrophobic effect, since it, like water, has a high cohesive energy.[2] Also, the standard free energies, enthalpies, and entropies of solution for several nonpolar gases in EAN parallel those in water.[1a] However, the heat capacities for solution of alcohols in EAN and water differ markedly, reflecting the fact that water, but not EAN, undergoes a fluctuation between hydrogen-bonded forms of different geometry and density.[2]

Water has been used beneficially as a solvent for the Diels-Alder reaction,[6] one of the most useful reactions in organic synthesis. Dramatic rate and stereoselectivity enhancements have been observed in water relative to those obtained in conventional organic solvents.[6] Since it shares some of the properties of water, we have begun a study to determine if EAN can also serve as a useful solvent for the Diels-Alder reaction. Herein we present our initial results.

The reactions of cyclopentadiene (**1**) with methyl acrylate (**2a**) and methyl vinyl ketone (**2b**) to give endo (**3**) and exo (**4**) cycloaddition products[7] were performed (eq 1). The results for the former reaction are summarized in Table I. A solution of 0.20 M **1** and 0.20 M **2a**[8] in EAN was stirred at 25 °C for 72 h and extracted with hexane, and rotary-evaporation of the extracts at 25 °C left a 98%



(1)

1 **2** **3** **4**

a, X = CO_2Me; **b**, X = COMe

yield of **3a** and **4a** with a **3a**:**4a** ratio of 6.7, as determined by GLC analysis.[9] The kinetics of the reaction in EAN were studied at 20.0 °C under pseudo-first-order conditions with 0.010 M **1** and 0.20 M **2a**. The appearance of **3a** and **4a** was followed by GLC analysis, with hexadecane as an internal standard, of isolated products obtained by hexane extraction of aliquots of the reaction mixture. The resultant pseudo-first-order rate constant, 1.7×10^{-5} sec^{-1}, gave the second-order rate constant, k_2, listed in Table I. For comparison, the kinetics of the reaction in water at 21 °C under pseudo-first-order conditions were determined with 0.40 mM **1** and 12 mM **2a** by following the disappearance of **1** by UV spectroscopy at 250 nm.[6a] The **3a**:**4a** ratio in water depends on the conditions used, and values from 5.3 to 9.3 have been reported by Breslow and co-workers[6c] and Lattes and co-workers.[10] Table I also contains k_2 for the reaction of **1** with **2a** at 35 °C in a nonpolar organic solvent, 1-bromobutane,[7a] and **3a**:**4a** values for the same reaction in benzene,[7a] ethanol,[11] methanol,[11] and formamide.[10]

The k_2 values in EAN and water at 20.0 °C are 3.2 and 57 times greater, respectively, than that in 1-bromobutane at 35 °C. Thus, the use of EAN gives a rate enhancement, but it is considerably less than that obtained in water. On the other hand, the **3a**:**4a** ratios in both EAN and water are greater than those in benzene and ethanol, and the ratios in EAN, methanol, and formamide are about the same.

A solution of 0.20 M **1** and 0.20 M **2b** (freshly distilled) in EAN was stirred at 25 °C for 72 h and worked up and analyzed as for the reaction of **1** and **2a** in EAN. A **3b**:**4b** ratio of 10 resulted. However, the yield of **3b** and **4b** was only 45%, and it did not improve with the addition of 2.5 mM 4-*tert*-butylcatechol. At present the reason for the low yield of **3b** and **4b** is unclear. Breslow and co-workers obtained **3b**:**4b** ratios of 21.4, 10.4, 8.9, 8.5, and 3.85 in water, ethylene glycol, formamide, ethanol, and **1**, respectively.[6c,12]

The rate and endo selectivity enhancements for Diels-Alder reactions in water have been attributed largely to hydrophobic association of reactants, based on salt effects,[6d] and not to simple solvent polarity effects.[11] We have performed reactions of **1** with **2a** in EAN containing LiCl and LiI, and the results are summarized in Table I. The former salt had essentially no effect on k_2, whereas the latter tripled it. With each salt the **3a**:**4a** ratio increased modestly. In water, LiI is a chaotropic, and LiCl an antichaotropic agent,[12] and they would be expected to decrease and increase, respectively, both the rate and endo selectivity of a given Diels-Alder reaction, due to salting-in and salting-out effects. The origins of the salt effects in EAN are not clear. However, if the enhanced rate and endo selectivity in EAN derive from solvophobic effects, LiI acts to salt-out the organic reagents, opposite to its effect in water. Breslow and Guo[12] have observed related effects of chaotropic and antichaotropic agents in ethylene glycol and formamide on the Diels-Alder reaction of **1** with **2b**.

Formamide and ethylene glycol also exhibit some of the properties of water.[13] For example, single-chain surfactants form micelles in these solvents, but with cmc's that are greater than those in water by factors of *ca.*100 or more.[13] Since these factors are substantially larger than those noted above for EAN, one would expect solvophobic effects to be stronger in EAN than in formamide and ethylene glycol, even though a comparison of the above **3**:**4** values does not so indicate.

Table I. Diels-Alder Reactions of **1** and **2a**.[a]

solvent	T, °C	**1** concn, M	**2a** concn, M	added salt, 1.0 M	**3a**:**4a**	10^4k_2, $M^{-1}sec^{-1}$
EAN	25 ± 2	0.20	0.20		6.7	
EAN	20.0 ± 0.2	0.010	0.20		6.7	1.7
EAN	20.0 ± 0.2	0.010	0.20	LiCl	7.2	1.6
EAN	20.0 ± 0.2	0.010	0.20	LiI	7.4	5.4
water	21 ± 1	0.00040	0.012			30
water[b,c]	25	0.15 (0.30)	0.15 (0.30)		9.3 (5.9)	
water[c,d]	20	0.15 (0.30)	0.15 (0.30)		7.4 (5.3)	
1-chloro-butane[e]	35					0.53
benzene[e]	35	1.25	1.25		2.8	
ethanol[f]	30				5.2	
methanol[f]	26				7.0	
formamide[d]	20	0.15 (0.30)	0.15 (0.30)		6.7 (6.7)	

[a]The results from the current study are average values of at least duplicate runs with average deviations of ±0.1 and ±10% for the values of **3a**:**4a** and k_2, respectively. [b]Results from Ref. 6c. [c]The reaction mixtures were heterogeneous; formal concentrations are given. [d]Results from Ref. 10. [e]Results from Ref. 7a. [f]Results from Ref. 11; the exact concentrations of **1** and **2a** were not specified.

In summary, EAN gave endo selectivity enhancements for the reactions of **1** with **2a** and **2b**, and a rate enhancement for the former, relative to nonpolar organic solvents. Although the rate and endo selectivity enhancements in the present study are not as great as those in water, EAN should be superior to water as a reaction medium in at least one respect: in general, neutral organic compounds are more soluble in EAN than in water.[4b,14] Therefore, unlike the situation with the latter, reactions can be performed on a synthetically useful scale in EAN under homogeneous conditions with perhaps greater reproducibility from run to run. Also, EAN might prove appropriate for the Diels-Alder reactions of water-sensitive compounds.

CAUTION It has been reported that EAN is a potentially explosive compound under certain conditions.[2] Even though we and others have used EAN in a number of applications without problems,[15] and Mirejovsky and Arnett failed to denote it by hammering or heating,[2] it should be used with due caution.

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